(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 310 249 A1

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
14.05.2003 Bulletin 2003/20

(21) Application number: **02023126.2**

(22) Date of filing: **15.10.2002**

(51) Int Cl.[7]: **A61K 31/232**, A61K 31/202, A61P 9/00, A61P 9/04, A61P 9/10

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **12.11.2001 IT MI20012384**

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(54) **Use of polyunsatured fatty acids for the primary prevention of major cardiovascular events**

(57) The use of polyunsaturated fatty acids of the ω-3 series such as eicosapentaenoic acid (EPA, $C_{20:5}$ ω-3), docosahexaenoic acid (DHA, $C_{22:6}$ ω-3), or their pharmaceutically acceptable derivatives is described for the primary prevention of major cardiovascular events in subjects who have not undergone previous infarct episodes.

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Description

[0001] The invention relates to the use of polyunsaturated fatty acids for the primary prevention of major cardiovascular events.

[0002] In particular, the invention concerns the use of polyunsaturated fatty acids of the ω-3 series such as eicosapentaenoic acid (EPA, $C_{20:5}$ ω-3), docosahexaenoic acid (DHA, $C_{22:6}$ ω-3), or their pharmaceutically acceptable derivatives, either alone or mixed together, for the primary prevention of major cardiovascular events.

[0003] The beneficial effects of polyunsaturated fatty acids of the ω-3 series on multiple risk factors for cardiovascular illnesses are well known; for example the patents IT 1235879, US 5502077, US 5656667 and US 5698594 refer respectively to hypertriglyceridemia, defects of the cholesterol level and hypertension. However, each of the cited documents deal with the treatment of risk factors, not with real and proclaimed illnesses.

[0004] US 5753703 describes the use of L-carnitine or its derivatives in association with polyunsaturated fatty acids of the ω-3 series or their esters, in particular EPA and DHA, for the prevention and treatment of cardiovascular disorders, vascular pathologies, diabetic peripheral neuropathies, and atherosclerotic, thromboembolytic and tissue disorders.

[0005] EP-B-0409903 describes a process for preparing high concentration mixtures of EPA and DHA and/or their esters useful for treating hyperlipemia and related pathologies, thrombosis, cardiac infarct, platelet aggregation, as anticoagulants in the prevention of atherosclerosis, for the treatment of cerebral infarct, of lesions and occlusions caused by vasomotor spasms, of diabetes and its complications, of chronic and acute inflammations, of autoimmune symptoms, in the prevention of side effects caused by non-steroid anti-inflammatories at the gastrointestinal level and in tumour prevention.

[0006] CN 1082909 describes compositions based on ethyl esters of EPA and DHA and other polyunsaturated fatty acids of the ω-3 series in association with soya phospholipids, oenothera odorata and ginkgetin, as antithrombotic and antidementia agents for treating for example dementia and infarct of the myocardium.

[0007] US 5760081 describes a method for preventing imminent fibrillation of the myocardial ventricle by intravenous infusion of a composition containing EPA, where the subject at risk of imminent fibrillation has already often been the protagonist of an episode of infarct of the myocardium and where the infusion is effected within 3 hours of the infarct episode, possibly using intracardiac injection. These are always situations of extreme emergency and of parenteral intervention, for the specific treatment of ventricular fibrillation.

[0008] Swann et al., Clinical Drug Investigation 15 (6), 473, 1998 have also shown that the administration of EPA and DHA ethylesters, at a dose of 4 g per day, leads to a decrease in triglycerides and total apolipoprotein C III and to an increase in antithrombin III, in subjects with abnormal plasmatic lipoprotein symptoms and have undergone an infarct of the myocardium, they having consequently suggested that an administration of these compositions can result in an improvement in the lipoprotein level and hence a decrease in the relative risk factors.

[0009] WO 00/48592 describes the use of a mixture of EPA and DHA ethylesters in quantities greater than 25 wt.% for preventing death, in particular "sudden death" in patients who have already suffered an infarct of the myocardium. This therefore represents the use of said mixture in so-called secondary death prevention, i.e. in subjects who have already suffered infarct.

[0010] The prevention of cardiovascular damage by means of fatty acid mixtures described in the state of the art is therefore focused on "secondary" prevention of cardiovascular damage. i.e. aimed at protecting a subject who has already suffered an infarct, whereas "primary" prevention of major cardiovascular events, i.e. prevention in subjects who, while affected by various pathologies of the cardiocirculatory and/or cardiorespiratory systems, have not yet suffered an infarct episode, constitutes a technical problem which is still felt in this sector.

[0011] According to a first aspect the invention relates to the use of polyunsaturated fatty acids of the ω-3 series for the preparation of a drug useful in the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, wherein the fatty acids comprise eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) and/or at least one pharmaceutically acceptable derivative thereof, in quantities greater than or equal to 25 wt% on the total fatty acid weight.

[0012] In the present description, the expression "polyunsaturated fatty acids of the ω-3 series" means those long-chain polyunsaturated fatty acids, generally C_{16}-C_{24}, containing fish oils, in particular those having a C_{20}-C_{22} chain, which are predominant in purification processes.

[0013] The expression "major cardiovascular event" means in particular those events which involve reversible or irreversible cardiovascular damage, such as infarct of the myocardium and of individual coronary branches, death from cardiac causes, sudden death, etc., besides to infarct, broadly speaking, ictus etc., and those conditions prodromal to such major events, such as myocardial fibrillation, atrial and/or ventricular fibrillation, etc. Said major cardiovascular events are usually induced by various cardiocirculatory and cardiorespiratory pathologies such as coronary ischemic illness not displayed by previous infarct episodes, and by serious hypoxic/anoxic states caused by a sudden lack of oxygen (for example during anesthesia, surgery, etc.), possibly in the presence of conditions which contemplate an increase in the oxygen requirement (accentuated physical stress, drug abuse, acute hypertensive crises, etc.) and

analogous acute and chronic pathologies due to cardiac defects of electrical and/or mechanical type.

[0014] The subjects affected by pathologies of the cardiocirculatory and cardiorespiratory system, hence not simply at prospective risk due to hypertriglyceridemia, hypertension or other, are representative of subjects definable at various levels as cardiopaths, by being affected, for example, by coronary ischemia detectable by coronarography, scintigraphy of the myocardium, electrocardiogram (ECG) under stress, etc., against which interventions of revascularization (angioplasty) or other possible pharmacological or invasive treatments have been proposed, and of subjects affected by electrical hyperexcitability of the myocardium cells, disorder of the diffusion of electrical excitement or of electrical conduction (arrhythmia, fibrillation, etc.) or by other defects of mechanical type (cardiac insufficiency, decompensation), possibly aggravated by concomitant pathologies such as diabetes.

[0015] The use of polyunsaturated fatty acids of the ω-3 series according to the invention is particularly indicated if the occurrence of a major event is predicted, such as an infarct, in particular of the myocardium, death from a cardiological cause, or sudden death, and where such an occurrence takes place in cardiopathic subjects affected, for example, by coronary ischemia, arrhythmia, atrial and/or ventricular fibrillation, electrical hyperexcitability of the myocardium cells, disorder of the diffusion of electrical excitement or of electrical conduction of the myocardium, or cardiac disorders of mechanical type, for example cardiac insufficiency or cardiac decompensation, possibly affected by diabetic pathology concomitant with the cardiopathy.

[0016] Preferably, the content of EPA and/or DHA and/or of the at least one derivative thereof is between 50% and 100%, in particular between 75% and 95%, and more preferably about 85% by weight on the total fatty acid weight. The preferred EPA and/or DHA derivatives are selected from the corresponding C_1-C_3 alkyl esters and/or from their salts with pharmaceutically acceptable bases such as sodium hydroxide, lysine, arginine or aminoalcohols such as choline. The ethylesters of EPA and DHA, in particular mixed together in any concentration and percentage, are the most preferred.

[0017] The drug is administered preferably orally, in particular in the form of soft gelatin capsules. For oral use, the unit dose generally comprises 100-1000 mg of polyunsaturated fatty acids of the ω-3 series, preferably 500-1000 mg or 300-500 mg, the total dose being usually around 0.1-3.0 g per day or per alternate day, according to the case concerned, and preferably 0.3-2.0 g per day and in particular 1.0 g per day. The effective dose of the drug suitable for the use of the invention is 1.0-60.0 mg/kg of body weight/day.

[0018] Other types of formulation for oral administration are also suitable for the purposes of the invention; for example hard capsules or tablets, in which the polyunsaturated fatty acids are adsorbed on solid supports. It is also possible to use emulsions, granulates in dispersing excipients, syrups, droplets, etc., and other forms of administration able to ensure systemic absorption of the drug, such as sterile solutions or emulsions and the like, suitable for parenteral use and the like, as evaluated by the expert of the art, on the basis of the severity of the pathology.

[0019] Those compositions illustrated in the European Pharmacopea 2000 (EuPh. 2000), containing quantities greater than or equal to 80 wt% of mixtures of EPA and DHA ethylesters and a total of ω-3 polyunsaturated fatty acid ethylesters greater than or equal to 90 wt% are also suitable for the purposes of the present invention.

[0020] The aforestated compositions and the drugs suitable for the use of the invention can be prepared by methods known to the expert of the art, such as those described in US 5130061, WO 89/11521, IT 1235879, JP 02/25447, which are incorporated into the present description with regard to the method of preparation.

[0021] The drug suitable for use according to the present invention can also comprise other active principles and/or drugs, in association, possessing activity complementary to or synergic with that of the drug suitable for use according to the invention, and also at least one pharmaceutically acceptable vehicle and/or one diluent and/or one surfactant and/or one thickener and/or one binder and/or one lubricant and/or one aromatizer and/or one colorant and/or one stabilizer and the like, which can easily be selected by the expert of the art. Of the stabilizers, antioxidants such as vitamin E (tocopherol), ascorbyl palmitate, ascorbic acid, hydroxytoluene and the like, which can be easily selected by the expert of the art, are particularly preferred.

[0022] According to another aspect, the invention relates to a method for the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, comprising the administration of an effective dose of a drug comprising polyunsaturated fatty acids of the ω-3 series as hereinbefore described. In particular, the method of the invention is indicated whenever the occurrence of a major cardiac event is predicted such as an infarct, in particular of the myocardium, death from a cardiological cause or sudden death.

[0023] The following examples illustrate the invention but without limiting it.

[0024] The compositions illustrated in the following table were prepared by the methods described in US 5130061 (compositions A, C, D, F), IT 1235879 (composition B), JP 02/25447 (composition E) and WO 89/11521 (compositions G-I).

[0025] All the quantities indicated in the following table express percentages by weight on the total weight of polyunsaturated fatty acids of the ω-3 series.

	A[1]	B[1]	C[1]	D[1]	E[1]	F[1]	G[1]	H[2]	I[3]
EPA	>40	>44	>40	>25	>80	>20	<15	>40	>40
DHA	>34	>30	>34	>20	<10	>25	>80	>30	>30
EPA+DHA	>85	>80	>80	>50	>80	>50	>85	>80	>80
esters[4]		>3	-						
tot.esters[5]			>90						
α-tocopherol	0.03	0.03	0.1	0.3	0.1	0.3	0.03	0.1	0.1

[1]-ethyl esters; [2]-free acids; [3]-sodium salts; [4]-ethyl esters of other (C_{20}, C_{21}, C_{22}) ω-3 acids; [5]-total ethyl esters of ω-3 acids.

EXAMPLE 2

[0026] The compositions illustrated in the following table, relative to soft gelatin capsules containing 1 g of polyunsaturated fatty acid ethyl esters, were prepared by methods known in the art.

	A (mg)	B (mg)	C (mg)
EPA[1]	525	-	>400
DHA[1]	315	-	>340
EPA+DHA[1]		850	>800
Total ω-3[1]		-	>900
d-α-tocopherol	4 I.U.	-	4 I.U.
d,l-α-tocopherol		0.3	
gelatin	246	-	246
gelatin succinate		233	
glycerol	118	67	118
OFR OFG	2.27 1.27	-	2.27 1.27
SOB		1.09	
SPOB		0.54	

[1]-ethyl esters; OFR: red iron oxide OFG: yellow iron oxide; SOB: sodium p-oxybenzoate; SPOB: sodium propyl p-oxybenzoate; I.U.: international units.

PHARMACOLOGICAL ACTIVITY

[0027] The pharmacological activity of the compositions of the invention was evaluated on the basis of tests carried out on small laboratory animals (mouse, guinea pig, rat); this experimental model was chosen because of the ability to make rapid and highly reproducible verifications and to use a sufficiently large number of animals, such as to enable a statistically accurate evaluation of the results to be made without exposing the patient to risk, with evident ethical implications.

[0028] During the course of these tests, groups of animals were pretreated repeatedly with the formulations of Examples 1 and 2 and then, in comparison with untreated groups, were subjected to the action of cardiotoxic or respiration-depressive substances, then visually measuring protection against death, or - by means of elettrocardiographic recording - measuring the delay in the start of initial cardiac arrhythmia or of ventricular tachycardia and above all the delay in or the prevention of animal death due to sudden cardiac and/or respiratory arrest.

[0029] Using an analogous experimental model, cardiological pathology, coronary ischemia and a state of infarct were induced by coronary ligature instead of by cardiotoxic agents.

Test 1

[0030] The experimental sudden death model was obtained by cardiac arrest induced by intravenous (i.v.) administration of a cardiotoxic agent (ouabain).

[0031] In preliminary tests, various doses of ouabain were administered to non-anesthetized guinea pigs of both sexes of weight 300-380 g, in order to determine the minimum lethal dose for 100% of the animals within 15 minutes from i.v. injection (240 mg/kg, intravenously administered over 3 minutes).

[0032] Two groups of 20 guinea pigs were then treated with 50 and 100 mg/kg of a composition containing 85% of EPA and DHA ethylesters (Ex. 1, composition A) for 10 days. After 2 hours from the last administration the two groups of guinea pigs and a further untreated group, used as control, were treated with 240 mg/kg i.v. of ouabain, recording mortality within the subsequent 15 minutes.

[0033] Results expressed as survivors after 15 minutes:

Controls	00/20
50 mg/kg	11/20
100 mg/kg	16/20

Test 2

[0034] 3 groups of 15 male mice, initial weight 25-32 g, were treated orally for 15 days with physiological solution (control group) and with 50 or 100 mg/kg of a composition containing 85% of EPA and DHA ethylesters (Ex. 1, composition A).

[0035] 60 minutes after the end of the last treatment, the animals of all the groups were treated with sodium pentabarbital i.p. (50 mg/kg) and then with aconitine i.v. (0.25 mg/kg). The times of appearance of cardiac arrhythmia (deviation >5 seconds from the normal sinus rhythm), of ventricular fibrillation and of cardiac arrest were determined by electrocardiograph recording. Results expressed as mean ± standard deviation (seconds) on the positive animals.

T	t_1 (sec)	t_2 (sec)	t_3 (sec)	S
C	123 ± 12 (15/15)	174 ± 7 (15/15)	214 ± 32 (15/15)	00/15
50 mg/kg	168 ± 8 (08/15)	235 ± 16 (06/15)	350 ± 26 (06/15)	09/15
100 mg/kg	195 ± 15 (05/15)	284 ± 18 (03/15)	378 ± 35 (03/15)	12/15

[0036] T-treatment; t_1-time of appearance of arrhythmia (number of animals); t_2-time of appearance of fibrillation (number of animals); t_3-time of cardiac arrest (number of animals); S-survivors after 15 minutes; C-control (with physiological solution).

Test 3

[0037] 2 groups of 20 male rats, initial weight 310-350 g, were treated orally for 15 days with physiological solution (control group) and with 100 mg/kg of a composition containing >80% of EPA and DHA ethylesters (Ex. 1, composition B). The rats of the 2 groups were then anesthetized with sodium pentobarbital i.p. (50 mg/kg), then subjected to ligature of the left anterior descending coronary artery, which allows blood flow to the left ventricle, so inducing an acute ischemic state of the myocardium. During the subsequent 15 minutes the duration of ventricular fibrillation was recorded by ECG, this either resolving itself spontaneously or concluding with sudden death.

Results

[0038]

T	F (sec)	Mortality	S (%)
C	190 ± 24	16/20	20

(continued)

	(18/20)		
100 mg/kg	55 ± 5 (04/20)	01/20	95

[0039] T-treatment; F-duration of fibrillation; S-survivals after 15 minutes; C-control (with physiological solution).

Test 4

[0040] The experimental model implemented for sudden death by respiratory arrest involves its inducement by chloroform inhalation.

[0041] 4 groups of 10 male mice, initial weight 26-32 g, were treated orally for 5 days with physiological solution (control group) and with 10, 30 and 60 mg/kg of a composition containing 80% of EPA and DHA ethylesters (Ex. 1, composition C).

[0042] 60 minutes after the end of the last treatment, the animals were exposed to chloroform until respiratory arrest had occurred. The animals were then checked for tachyarrhythmia of the myocardium induced by the hypoxic state, this either resolving itself spontaneously within the next 15 minutes or concluding with death of the animal.

Results

[0043]

Treatment	Protection from tachyarrhythmia	Survivals
Control	00/10	03/10
10 mg/kg	04/10	06/10
30 mg/kg	07/10	08/10
60 mg/kg	09/10	10/10

Test 5

[0044] 2 groups of 20 male rats were treated as on Test 3, with physiological solution and with the same EPA and DHA composition (Example 1, composition B).

[0045] Ligature of the circumflex coronary artery was then effected, with consequent reduction in the contractile capacity of the myocardium and of the ejection fraction. The mortality of 18/20 animals of the control group fell to 4/20 of the treated group, during the course of the subsequent 60 minutes.

[0046] The clinical results of the tests demonstrate the pharmacological activity of the polyunsaturated fatty acids of the ω-3 series in the primary prevention of major cardiovascular events in subjects who have not undergone previous infarct episodes.

Claims

1. Use of polyunsaturated fatty acids of the ω-3 series for the preparation of a drug useful in the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, wherein the fatty acids comprise eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) and/or at least one pharmaceutically acceptable derivative thereof, in quantities greater than or equal to 25 wt% on the total fatty acid weight.

2. Use as claimed in claim 1, wherein the major cardiovascular event is infarct.

3. Use as claimed in claim 1, wherein the major cardiovascular event is infarct of the myocardium.

4. Use as claimed in claim 1, wherein the major cardiovascular event is death from a cardiological cause.

5. Use as claimed in claim 1, wherein the major cardiovascular event is sudden death.

6. Use as claimed in any one of the preceding claims, wherein the subjects are cardiopathic.

7. Use as claimed in any one of the preceding claims, wherein the subjects are affected by coronary ischemia.

8. Use as claimed in any one of the preceding claims, wherein the subjects are affected by arrhythmia, fibrillation, electrical hyperexcitability of the myocardium cells, disorder of diffusion of the electrical excitement and of electrical conduction of the myocardium.

9. Use as claimed in any one of the preceding claims, wherein the subjects are affected by cardiac disorders of mechanical type.

10. Use as claimed in any one of the preceding claims, wherein the subjects are affected by cardiac insufficiency.

11. Use as claimed in any one of the preceding claims, wherein the subjects are affected by cardiac decompensation.

12. Use as claimed in any one of claims from 6 to 11, wherein the subjects are affected by diabetic pathology concomitant with cardiopathy.

13. Use as claimed in any one of the preceding claims, wherein the content of EPA and/or DHA and/or of the at least one derivative thereof is between 50% and 100% by weight on the total fatty acid weight.

14. Use as claimed in any one of the preceding claims, wherein the content of EPA and/or DHA and/or of the at least one derivative thereof is between 75% and 95% by weight on the total fatty acid weight.

15. Use as claimed in any one of the preceding claims, wherein the content of EPA and/or DHA and/or of the at least one derivative thereof is equal to about 85% by weight on the total fatty acid weight.

16. Use as claimed in any one of the preceding claims, wherein the at least one derivative of EPA and/or DHA is selected from the corresponding C_1-C_3 alkyl esters and/or acids and/or salts with pharmaceutically acceptable bases.

17. Use as claimed in any one of the preceding claims, wherein the drug comprises EPA ethylester and/or DHA ethylester.

18. Use as claimed in any one of the preceding claims, wherein the drug is administered orally.

19. Use as claimed in any one of the preceding claims, wherein the drug is in the form of soft gelatin capsules.

20. Use as claimed in any one of the preceding claims, wherein the drug is administered at a dose of 0.1-3.0 g per day.

21. Use as claimed in any one of the preceding claims, wherein the drug is administered at a dose of 0.3-2.0 g per day.

22. Use as claimed in any one of the preceding claims, wherein the drug is administered at a dose of 1.0 g per day.

23. A method for the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, comprising the administration of an effective dose of a drug claimed in any one of the preceding claims.

24. A method as claimed in the preceding claim, wherein the major cardiovascular event is infarct.

25. A method as claimed in claim 23, wherein the major cardiovascular event is infarct of the myocardium.

26. A method as claimed in claim 23, wherein the major cardiovascular event is death from a cardiological cause.

27. A method as claimed in claim 23, wherein the major cardiovascular event is sudden death.

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 02 02 3126

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
P,X	EP 1 157 692 A (QUATEX NV) 28 November 2001 (2001-11-28) * claims 1,9,24,27-30 * * paragraph '0024! - paragraph '0026! * * paragraph '0091! - paragraph '0092! * ---	1-6, 8-11, 13-27	A61K31/232 A61K31/202 A61P9/00 A61P9/04 A61P9/10
X,D	EP 0 780 124 A (SIGMA TAU IND FARMACEUTI) 25 June 1997 (1997-06-25) * claim 1 * * column 1, paragraph 10 - paragraph 58 * ---	1,9, 12-23	
X	US 5 760 081 A (HALLAQ HAIFA ET AL) 2 June 1998 (1998-06-02) * column 1, line 16 - line 60 * --- -/--	1,5,6,8, 13-16, 20-23	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 February 2003	Bonzano, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

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INCOMPLETE SEARCH SHEET C

Application Number
EP 02 02 3126

Although claims 23-27 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
none

Claim(s) searched incompletely:
1-27

Reason for the limitation of the search:

Claims 1,6-23 relate to the treatment of diseases and to patients having underlying disorders, which are actually not well defined. The use of the definition "major cardiovascular event, electrical hyperexcitability of the myocardium cells, disorder of diffusion of the electrical excitement and of electrical conduction of the myocardium, cardiac disorder of mechanical type" in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search not fully possible.
Present claims 1-15,17-27 relate to an extremely large number of possible compounds (derivatives thereof). Support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Moreover, the expression "acids" as derivatives of EPA and/or DHA (claim 16) is not clear.
Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds EPA, DHA and their C1-C3 alkyl esters, mentioned in claims 1,16-17 for the therapeutic applications mentioned in claims 2-5 (in relation to the treatment of patients as defined in claims 1 and 6-12, 23 as far as clear), and 24-27.

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 02 3126

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WO 01 60778 A (BRIGHAM & WOMENS HOSPITAL) 23 August 2001 (2001-08-23) * page 1, line 1 - line 18 * * claims 13,18,23,24 * * page 20, line 27 - line 30 *	1,4-9, 13-16, 18, 20-23, 26,27	
A	WO 00 32210 A (LANGHOFF WOLFGANG ;LAUMANN UDO (DE)) 8 June 2000 (2000-06-08) * page 1, line 34 - page 2, line 2 * * claim 14 *		
A	PAKALA, R. ET AL: "Vascular smooth muscle cells preloaded with eicosapentaenoic acid and docosahexaenoic acid fail to respond to serotonin stimulation" ATHEROSCLEROSIS (SHANNON, IRELAND) (2000), 153(1), 47-57 , XP002229283		TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	TAKEO, SATOSHI ET AL: "Effects of long-term treatment with eicosapentaenoic acid on the heart subjected to ischemia/reperfusion and hypoxia/reoxygenation in rats" MOLECULAR AND CELLULAR BIOCHEMISTRY (1998), 188(1&2), 199-208 , XP008012809 * page 199, column 1 *	1,2	
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EPO FORM 1503 03.82 (P04C10)

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 02 3126

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	SINGH, RAM B. ET AL: "Randomized, double-blind, placebo-controlled trial of fish oil and mustar oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival-4" CARDIOVASCULAR DRUGS AND THERAPY (1997), 11(3), 485-491 , XP008012824 * page 491 * * page 487, column 2, paragraph 2 *	1,2	
X	GUALLAR, ELISEO ET AL: "Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study" ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY (1999), 19(4), 1111-1118 , XP001134928 * page 1112, column 1, paragraph 3 - paragraph 4 * * page 1117, paragraph 2 *	1,2	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	MCLENNAN, PETER ET AL: "The cardiovascular protective role of docosahexaenoic acid" EUROPEAN JOURNAL OF PHARMACOLOGY (1996), 300(1/2), 83-9 , XP001134929 * page 88, column 2, paragraph 3 *	1,2	
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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	RISSANEN TIINA ET AL: "Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: The Kuopio Ischaemic Heart Disease Risk Factor Study." CIRCULATION, vol. 102, no. 22, 28 November 2000 (2000-11-28), pages 2677-2679, XP001134935 ISSN: 0009-7322 * page 2678, column 1, paragraph 3 - column 2, paragraph 2 * ---	1,2	
X	RISSANEN T H (REPRINT) ET AL: "Fish oil derived fatty acids, docosahexaenoic acid and docosapentaenoic acid and the risk of acute myocardial infarction" CIRCULATION, (27 OCT 1998) VOL. 98, NO. 17, SUPP. 'S!, PP. 2823-2823. PUBLISHER: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436. ISSN: 0009-7322., XP008012807 UNIV KUOPIO, FIN-70211 KUOPIO, FINLAND * abstract * -----	1,2	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 02 3126

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

19-02-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1157692 A	28-11-2001	EP 1157692 A1	28-11-2001
		PL 347655 A1	03-12-2001
EP 0780124 A	25-06-1997	IT RM950835 A1	23-06-1997
		AT 210977 T	15-01-2002
		CA 2191645 A1	22-06-1997
		DE 69618158 D1	31-01-2002
		DE 69618158 T2	18-07-2002
		DK 780124 T3	15-04-2002
		EP 0780124 A1	25-06-1997
		ES 2169197 T3	01-07-2002
		JP 9176005 A	08-07-1997
		PT 780124 T	28-06-2002
		US 5753703 A	19-05-1998
		ZA 9610769 A	09-07-1997
US 5760081 A	02-06-1998	NONE	
WO 0160778 A	23-08-2001	AU 3846801 A	27-08-2001
		WO 0160778 A2	23-08-2001
		US 2002055538 A1	09-05-2002
WO 0032210 A	08-06-2000	DE 19855426 A1	08-06-2000
		WO 0032210 A1	08-06-2000
		EP 1135146 A1	26-09-2001

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82